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RESEARCH ARTICLE

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Migraine and the risk of all-cause dementia, Alzheimer's disease, and vascular dementia: A prospective cohort study in community-dwelling older adults

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Objectives: Dementia is the most common neurological disease in older adults; headaches, including migraines, are the most common neurological disorder across all ages. The objective of this study was to explore the relationship between migraines and dementia, including Alzheimer's disease (AD) and vascular dementia (VaD).

Methods: Analyses were based on 679 community-dwelling participants 65+ years from the Manitoba Study of Health and Aging, a population-based, prospective cohort study. Participants screened as cognitively intact at baseline had complete data on migraine history and all covariates at baseline and were assessed for cognitive outcomes (all-cause dementia, AD, and VaD) 5 years later. The association of exposure (lifetime history of migraines), confounding (age, gender, education, and depression), and intervening variables (hypertension, myocardial infarction, other heart conditions, stroke, and diabetes) with all-cause dementia and dementia subtypes (AD and VaD) was assessed using multiple logistic regression models.

Results: A history of migraines was significantly associated with both all-cause dementia (odds ratio [OR]=2.97; 95% confidence interval [CI]=1.25-6.61) and AD (OR=4.22; 95% CI=1.59-10.42), even after adjustment for confounding and intervening variables. Migraines were not significantly associated with VaD either before (OR=1.83; 95% CI=0.39-8.52) or after (OR=1.52; 95% CI=0.20-7.23) such adjustment.

Conclusions: Migraines were a significant risk factor for AD and all-cause dementia. Despite the vascular mechanisms involved in migraine physiology, migraines were not significantly associated with VaD in this study. Recognition of the long-term detrimental consequences of migraines for AD and dementia has implications for migraine management, as well as for our understanding of AD etiology.

KEYWORDS

Alzheimer disease, Canada, cohort studies, dementia, headache, logistic models, migraine disorders, odds ratio, risk factors, vascular dementia

1 | INTRODUCTION

As the global population ages, the prevalence of age-related conditions, such as dementia, will continue to rise.[1] Although dementia is the most common neurological disease in older adults, headaches are the most common neurological disorder across all ages, affecting almost half of the global population of adults.[2] Migraines are the most debilitating form of headaches, affecting 20% of women and 8% of men.[3] Both neurological disorders—dementia and migraines—cause significant impacts on individuals and their families, as well as on

society more broadly. The relationship between migraines and dementia, including Alzheimer's disease (AD) and vascular dementia (VaD), has not yet been clearly established and has the potential to inform prevention and treatment as well as further understanding of the etiology of these disorders.

Cognitive consequences of migraines have been more thoroughly studied for cognition in general than for cognitive states such as dementia. Although one systematic review concluded that migraines were associated with mild cognitive changes across several domains,[4] particularly in patient populations, other reviews[5,6] focusing on stronger cohort study designs have concluded that current evidence does not support an association between migraines and cognitive decline. However, evidence is less clear on the impact of migraines on dementia. A recent meta-analysis[7] of the limited number of cohort studies available noted substantial heterogeneity in these studies. Overall, it concluded that migraines did not increase the risk of dementia, although it did find an association with the broader category of headache disorders. An earlier meta-analysis of four case-control studies found a marginally significant inverse relationship between migraines and AD.[8] In contrast, results from individual studies have suggested that migraines significantly increase the risk of dementia, but that the effect may be restricted to specific subgroups (eg, women[9]) or subtypes of dementia (eg, VaD[10]), or that headache disorders broadly[11] or nonmigrainous headaches[12,13] may be risk factors rather than migraines specifically. Evidence of a significant association between migraines and dementia has been primarily based on patient populations, which are susceptible to selection biases.

The purpose of this study was to determine if migraines are a risk factor for dementia and its subtypes, AD and VaD, in a population-based prospective cohort study of community-dwelling older adults. The impact of possible intervening variables—hypertension, myocardial infarction, other heart conditions, stroke, and diabetes—was also investigated.

Key points

- Evidence of an association between migraines and dementia is unclear and may vary by dementia subtype, headache/migraine measure, gender, comorbidities, and clinical vs. community-based sample.
- A history of migraines was a significant risk factor for Alzheimer's disease and for all-cause dementia, even after adjustment for confounding and intervening variables in a community-dwelling population of older adults.
- A history of migraines was not significantly associated with vascular dementia.

2 | METHODS

2.1 | Sample

The Canadian Study of Health and Aging (CSHA) is a population-based, prospective study of aging and dementia in Canada.[14] Analyses were based on data from the Manitoba Study of Health and Aging (MSHA), a parallel study to the CSHA that used similar methods for data collection and diagnoses, but expanded sampling in the province of Manitoba, Canada.[15,16] The community sample of the MSHA was derived by random sampling from the provincial health insurance list of adults 65 years and older. This list is one of the most complete sampling frames available because the provincial health insurance plan provides almost universal coverage. Those excluded had federal health coverage (members of the Royal Canadian Mounted Police, the military, and First Nations [North American Indian] living on reserves) or resided in a remote, sparsely inhabited region. The study population was stratified by health region and age group (65-74, 75-84, and >85 years), and the two oldest age groups were oversampled to ensure sufficient numbers of older participants. At baseline (1991/1992), 2890 people were contacted to be interviewed; 1751 people were eligible and agreed to participate (see Figure 1). The Modified Mini-Mental State Exam (3MS) was used to screen for cognitive impairment; participants scoring less than 78 on the 3MS were invited for an in-depth clinical examination. Intact cognition was defined as screening above the cutpoint on the 3MS or below the cutpoint but subsequently assessed without dementia or any lesser impairment (cognitive impairment no dementia or CIND)[17] at clinical examination.

At baseline, 1355 participants were cognitively intact and constituted the incidence cohort. Age, gender, and education were determined during this baseline interview; a questionnaire on lifetime medical history, including history of migraines, was left with participants to be returned by mail (n=1039; 76.7%). The sample for this study was reduced from 1039 to 961 because of missing data on key MSHA-1 variables (education n=19; lifetime histories of migraine n=23, depression n=23, myocardial infarction n=25, other heart conditions n=37, stroke n=20, diabetes n=20, and hypertension n=26). Missing data for each variable were not mutually exclusive. In addition, 37 participants with CIND at follow-up were excluded as they neither met criteria for dementia nor for the cognitively intact comparison group. The analytic sample was thus based on 679 individuals who screened cognitively intact at baseline, provided data on migraine history and potential confounders, and completed the cognitive assessment at follow-up 5 years later (Figure 1). At follow-up, dementia diagnoses were determined based on clinical examination, with all-cause dementia diagnosed according to DSM-IV criteria,[18] AD according to NINCDS-ADRDA criteria,[19] and VaD according to NINDS-AIREN.[20,21]

2.2 | Statistical analysis

T tests with Satterthwaite's unequal variance assumption and Pearson chi-square tests, with Fisher's exact tests as appropriate, were used to

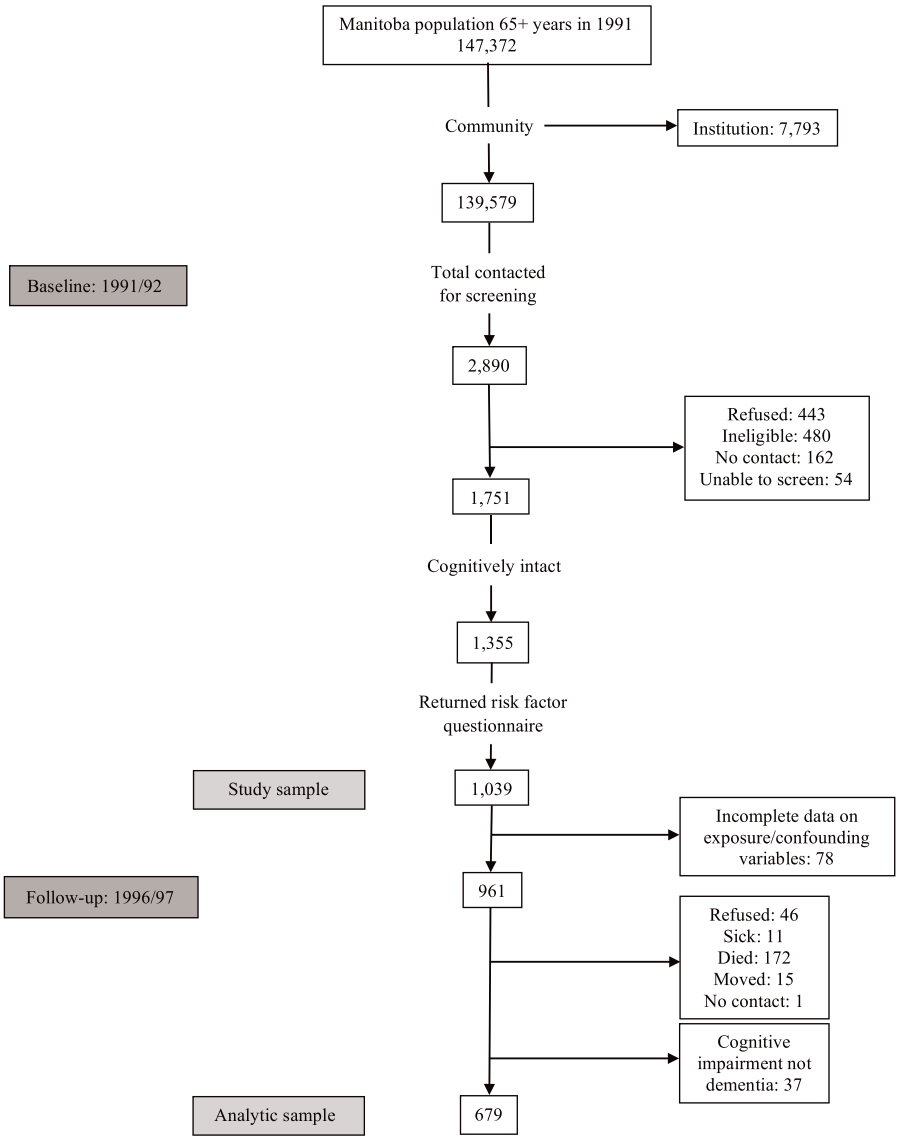

FIGURE 1 Manitoba Study of Health and Aging study population and derivation of the analytic sample [Colour figure can be viewed at wileyonlinelibrary.com]

analyze bivariate associations. The association of exposure (history of migraines), confounding (age, gender, education, and depression), and intervening variables (hypertension, myocardial infarction, other heart conditions, stroke, and diabetes) with dementia, AD, and VaD was analyzed using logistic regression models. Confounding and intervening variables assessed in the models were chosen based on supporting literature (eg, depressive symptoms are associated with dementia[22] and major depression increases the risk of migraine, while, in turn, migraine increases the risk of major depression.[23]) These variables remained in the final models if they met levels of statistical significance appropriate for regression modeling (alpha $\leq$.15 for main effects and $\leq$.05 for interaction terms).[24] Standard diagnostics (eg, multicollinearity and residual diagnostics) were conducted to assess model fit. First-order interactions between migraine history and each of the potential confounding and intervening variables (age, gender, education, depression, diabetes, hypertension, stroke, heart attack, or other heart condition) were assessed for dementia and AD, but not for VaD because of the limited number of VaD cases. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

2.3 | Standard protocol approvals, registrations, and patient consents

The Faculty of Medicine Committee on the Use of Human Subjects in Research at the University of Manitoba approved the original MSHA and MSHA-2. The present study received ethics approval from the Office of Research Ethics at the University of Waterloo.

3 | RESULTS

The sample was predominantly women (61.9%) with a mean age of 75.9 years (SD=6.1). At follow-up 5 years later, 7.5% (n=51) of participants had developed dementia, 5.1% (n=34) had developed AD, and

1.9% (n=12) had developed VaD. No men reporting a history of migraines were diagnosed with dementia. In bivariate analyses (Table 1), migraines were significantly associated with AD: a history of migraines was noted in 23.5% of participants with AD compared with 9.9% of cognitively intact participants (p=.01). Compared with cognitively intact participants, those with dementia, AD, or VaD were significantly older, and those with dementia or AD had significantly less education. Stroke was significantly more common in participants with dementia or VaD than in those who were cognitively intact. The association of other heart conditions with VaD was marginally significant (.05≤p<.10).

TABLE 1 Bivariate analyses of the association of cognitive health outcomes with exposure, confounding and intervening variables in the Manitoba Study of Health and Aging

	Intact Cognition[a]	Dementia	AD	VaD
	(n=628)	(n=51)	(n=34)	(n=12)
Variables	(%)	(%)	(%)	(%)
Exposure				
History of migraines	9.9	19.6	23.5*	16.7
Confounding variables				
Age, mean (SD)	75.1 (5.7)	81.5*** (5.3)	81.5*** (5.6)	81.7** (5.5)
Age				
65-74 years	45.5	11.8***	11.8***	16.7**
75-84 years	48.3	56.9	55.9	50.0
85+ years	6.2	31.4	32.4	33.3
Gender				
Female	61.5	66.7	67.7	66.7
Educational level				
Did not complete primary school	6.9	19.6	23.5	16.7
Completed primary school	47.8	45.1*	44.1**	58.3
Completed high school	27.4	21.6	14.7	25.0
Completed college/ university	18.0	13.7	17.7	0
Depression[b]	8.6	11.8	8.8	25.0
Intervening variables[b]				
Hypertension	31.7	41.2**	35.3	50.0***
Diabetes	6.4	9.8	11.8	0
Stroke	4.3	13.7	5.9	33.3
Myocardial infarction	8.0	9.8	8.8	8.3
Other heart condition	16.6	23.5	17.7	41.7

Abbreviations: AD: Alzheimer's disease; VaD: vascular dementia.

[a]Excludes cognitively impaired, not demented.

[b]Self-reported lifetime history (presence).

Comparison to cognitively intact group:

*p<.05.

**p<.01.

***p<.001.

Individuals with dementia were twice as likely (odds ratio [OR] = 2.23; 95% confidence interval [CI] = 1.06-4.66) as those without dementia to have a history of migraines in unadjusted models (Table 2). After adjustment for confounding by age and education, the association between migraines and dementia strengthened (OR=3.28; 95% CI = 1.41-7.21). Although stroke was not an independent statistically significant predictor of dementia, it met statistical criteria to enter the model and affected the strength of the association between migraines and dementia; it was thus included in the fully adjusted model. This full model indicated that individuals with dementia were three times more likely (OR=2.97; 95% CI=1.25-6.61) than nondemented individuals to have a history of migraines (Table 2).

AD was significantly associated with a history of migraines in unadjusted models (OR=2.81; 95% CI=1.22-6.47) (Table 3). After adjustment for age and education, those with AD were four times more likely to have a history of migraines (OR=4.22; 95% CI=1.59-10.42). None of the putative intervening variables contributed significantly to the model. No significant interactions were observed in either dementia or AD models.

VaD was not significantly associated with a history of migraines in either unadjusted models (OR=1.83; 95% CI=0.39-8.52) or models adjusted for significant confounding by age and depression (OR=2.21; 95% CI=0.32-9.77) (Table 4). When history of stroke was included in the model, however, the association between migraines and VaD weakened (OR=1.52; 95% CI=0.20-7.23), suggesting that stroke was an intervening variable. Stroke was also a significant independent predictor of VaD.

4 | DISCUSSION

Identifying risk factors for dementia may facilitate early identification of at-risk individuals and preventive strategies. Migraines were a significant risk factor for the development of all-cause dementia and AD in this study. The significant association between migraines and dementia may be driven by the strong association between migraines and AD. This interpretation is supported by the weaker association for dementia than for AD, reflecting a dilution of the association with migraines across all types of dementia including VaD, where a significant association was not found. However, the limited number of VaD cases in our study precludes firm conclusions on the association between migraines and VaD.

The significant increased risk of dementia with migraines noted in this study is consistent with those of other cohort studies[9,11,13] and in contrast with other individual studies[12] and a meta-analysis of cohort studies[7] that found no association. Additional evidence supports an association of dementia with headaches overall (including

TABLE 2 Association of migraine history with dementia in the Manitoba Study of Health and Aging: Adjusted and unadjusted logistic regression models

	Dementia		
	Unadjusted	Adjusted for Confounding Variables	Adjusted for Confounding and Intervening Variables
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Exposure			
Migraine history	**2.23 (1.06-4.66)**	**3.28 (1.41-7.21)**	**2.97 (1.25-6.61)**
Confounding variables			
Age			
65-74 years		1.0 (reference)	1.0
75-84 years		**4.36 (1.89-11.90)**	**4.21 (1.82-11.58)**
85+ years		**21.94 (8.24-66.06)**	**20.60 (7.73-62.06)**
Gender (male vs. female)		ns	ns
Educational level			
Did not complete primary school		1.0	1.0
Completed primary school		0.41 (0.18-1.01)	0.41 (0.17-1.01)
Completed high school		**0.32 (0.12-0.87)**	**0.32 (0.12-0.86)**
Completed college/university		**0.30 (0.10-0.88)**	**0.32 (0.10-0.94)**
Depression[a]		ns	ns
Intervening variables[a]			
Hypertension			ns
Diabetes			ns
Stroke			2.52 (0.90-6.42)
Heart attack			ns
Other heart condition			ns

Note. n=679. Bolded values indicate statistically significant results.

Abbreviations: CI: confidence interval; ns: not significant for inclusion in model (α>.15 for main effects); OR: odds ratio.

[a]Self-reported lifetime history (presence vs. absence).

migraines)[7,11] and nonmigrainous headaches.[12,13] However, the association between migraines and dementia was significant only among women in models stratified by gender[9]: this same gender effect was observed for all headaches[25] and nonmigrainous headaches.[13] The present study reflected this strong association of migraines with dementia in women; it was unable to assess potential gender differences because no male participants had dementia as well as a history of migraines.

Relatively few studies have focused on the association between migraines and subtypes of dementia, with reports of no association of AD with migraines[10,12] or nonmigrainous headaches[13] contrasting with the increased risk of AD with migraines seen in the current study. The current study builds on a previous overview of multiple risk factors for AD[26] that reported an association between migraines and AD in the same data source by focusing in this study on migraine, expanding the analysis to assess additional confounding variables and investigate possible intervening variables and interactions, and extending the outcomes examined to include VaD and all-cause dementia. For VaD, our lack of an association with migraines was consistent with some[11,12] but not all reports.[10] Effect modification by gender may occur in these dementia subtypes as noted for all-cause dementia. An early meta-analysis of case-control studies[8] found an overall inverse relationship between AD risk and migraines, with the association reaching significance only among women in three pooled studies. In contrast, although Tyas et al[26] also noted a significant and stronger association between migraines and AD in women, the risk of AD was higher rather than lower in women. However, gender differences with AD were not seen in a population-based linkage study.[10] It also did not find gender differences for VaD but did for mixed dementia, with headaches a significant risk factor in men but not in women. While significant associations between various definitions of headaches/migraines and dementia subtypes other than VaD and AD were found across a series of studies based on a health insurance database in Taiwan,[11,13,25] interpretation of this subtype is unclear. In one study,[25] this other dementia category excluded AD and VaD yet contributed almost all of the dementia cases. Other studies using the same database[11,13] defined their other dementia subtype based simply on exclusion of VaD and did not classify it further by AD. However, based on results from Yin et al,[25] this dementia category would similarly be expected to be predominantly non-AD dementia,

TABLE 3 Association of migraine history with Alzheimer's disease in the Manitoba Study of Health and Aging: Adjusted and unadjusted logistic regression models

	Alzheimer's Disease		
	Unadjusted	Adjusted for Confounding Variables	Adjusted for Confounding and Intervening Variables
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Exposure			
Migraine history	**2.81 (1.22-6.47)**	**4.22 (1.59-10.42)**	**4.22 (1.59-10.42)**
Confounding variables			
Age			
65-74 years		1.0 (reference)	1.0
75-84 years		**4.16 (1.51-14.67)**	**4.16 (1.51-14.67)**
85+ years		**23.03 (7.12-90.12)**	**23.03 (7.12-90.12)**
Gender (male vs. female)		ns	ns
Educational level			
Did not complete primary school		1.0	1.0
Completed primary school		0.35 (0.14-0.99)	0.35 (0.14-0.99)
Completed high school		**0.18 (0.05-0.61)**	**0.18 (0.05-0.61)**
Completed college/university		0.32 (0.09-1.05)	0.32 (0.09-1.05)
Depression[a]		ns	ns
Intervening variables[a]			
Hypertension			ns
Diabetes			ns
Stroke			ns
Heart attack			ns
Other heart condition			ns

Note. n=662. Bolded values indicate statistically significant results.

Abbreviations: CI: confidence interval; ns: not significant for inclusion in model (α>.15 for main effects); OR: odds ratio.

[a]Self-reported lifetime history (presence vs. absence).

raising issues of generalizability to other populations where AD would be a more common contributor to the prevalence of dementia.

Diagnostic criteria for exposures and outcomes may also affect whether a significant relationship between migraines and dementia is found. The studies used in the case-control meta-analysis for AD[8] used a wide variety of self-report migraine criteria, ranging from severe headaches to migraines, with one study validating self-reports with medical records. The current study studied migraines rather than headaches and relied on self-report for this condition. Both headaches and migraines were investigated in Hagen et al.[10] They found no significant association with AD. As reported elsewhere,[12] the comparison group in this study[10] was problematic in that participants did not complete a cognitive assessment to determine if they were free of dementia or other cognitive impairment. Their AD cases would thus be more similar to their comparison group, and this may have contributed to the lack of significant association between migraines and AD in their study. However, this would not explain why they found a significant association with VaD while we did not. Hagen et al[10] had a larger sample size for VaD than our study and thus greater statistical power to detect an association. Another explanation may be that the association found in their study was affected by not fully accounting for the effects of stroke, consistent with the weakening of the association between migraines and VaD in our study after adjustment for stroke. In addition, as the authors note, the significant association with VaD may reflect bias, because those with headaches or migraines may be more likely to seek medical care, and thus also more likely to be diagnosed with dementia.[10] Since their study linked headache/migraine reports with a dementia registry, this may have created an association between headaches and dementia.

Thus, in addition to the influences of gender, dementia subtype, and headache/migraine measure, differences in results may reflect the different sources used to recruit subjects. Unlike the current study, other studies have included patient populations, either directly[8,10,12] or through health insurance databases.[9,11,13,25] Patient populations would disproportionately include those with more severe migraines, as they would be more likely to seek medical attention for management of their migraines. More severe migraines would also be more likely to be associated with dementia than milder migraines, assuming that there is a causal association between migraines and dementia. Our study was not vulnerable to this bias because participants were assessed for dementia as part of the study and not through their interaction with the health care system.

TABLE 4 Association of migraine history with vascular dementia in the Manitoba Study of Health and Aging: Adjusted and unadjusted logistic regression models

	Vascular Dementia		
	Unadjusted	Adjusted for Confounding Variables	Adjusted for Confounding and Intervening Variables
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Exposure			
Migraine history	1.83 (0.39-8.52)	2.21 (0.32-9.77)	1.52 (0.20-7.23)
Confounding variables			
Age group			
65-74 years		1.0 (reference)	1.0
75-84 years		3.04 (0.69-21.00)	2.87 (0.64-20.09)
85+ years		**17.38 (3.16-133.44)**	**14.28 (2.46-112.64)**
Gender (male vs. female)	ns		ns
Educational level			
Did not complete primary school	ns		ns
Completed primary school	ns		ns
Completed high school	ns		ns
Completed college/university	ns		ns
Depression[a]		3.51 (0.73-13.03)	2.95 (0.57-11.61)
Intervening variables[a]			
Hypertension			ns
Diabetes			ns
Stroke			**7.90 (1.82-29.71)**
Heart attack			ns
Other heart condition			ns

Note. n=640. Bolded values indicate statistically significant results.

Abbreviations: CI: confidence interval; ns: not significant for inclusion in model (α>.15 for main effects); OR: odds ratio.

[a]Self-reported lifetime history (presence vs. absence).

The overlap between the underlying biological mechanisms of migraines and dementia suggests that migraines may increase the risk of dementia. Vascular risk factors and events, such as diabetes, hypertension, heart attacks, and stroke, are related to the development of dementias, including AD.[20,27-29] A relationship between vascular risk factors and migraines has also been observed.[30-32] Migraines, in turn, are also a risk factor for various diseases and disorders, such as cardiovascular disease.[31,33] Many of the mechanisms involved in migraine neurophysiology, such as inflammation and reduced cerebral blood flow, are also underlying causes of dementia.[34-36] Repeated activation of these pathways in chronic migraineurs has been shown to cause permanent neurological and vascular damage.[35] The extent of this damage may be related to the severity and frequency of migraine attacks; the varying levels of neurological damage may be similarly correlated with severity of dementia.[37,38] Migraines have been linked to white matter abnormalities,[39] although they may not modify the association between migraines and cognition.[40] Thus, vascular factors were hypothesized in our study to be intervening variables in the association between a history of migraines and dementia. However, while an association of migraines with all-cause dementia and AD was observed in this study, it did not appear to be explained by vascular dysfunction in the brain, as vascular variables did not influence this association.

An alternative explanation for the relationship between migraines and AD is that long-term neurological damage from migraines and subsequent development of late-life adverse cognitive outcomes may be specific to cognitive domains affected by migraine neurophysiology. Clarification of the cognitive domains affected by migraines may aid in determining vulnerability to specific types of cognitive impairment in late life. A greater understanding of the effect of migraine neurophysiology on cognitive function and decline has important clinical implications including identifying, screening, and providing preventive treatments for at-risk individuals.

Examining the vascular aspects of long-term migraine neurophysiology may clarify associations of migraine neurophysiology with stroke and VaD. Individuals with cardiovascular risk factors are at high risk for stroke and VaD. Stroke was a significant risk factor for VaD, consistent with previous reports and diagnostic criteria for VaD.[29,41] Furthermore, migraines have been reported to be a significant risk factor for stroke,[31,32,36] which was also found in our study (data not shown). A history of migraines was not a significant risk factor for VaD in this study, despite the vascular mechanisms involved in

migraine biology. This is consistent with our results that suggest vascular factors are not involved in the association between migraine and AD. The lack of a significant association between VaD and migraines may reflect the lack of a direct link between migraines and VaD and indicate that stroke is an intervening variable. We did see stronger intervening effects of vascular factors for VaD than for AD or overall dementia. However, although the association slightly weakened after inclusion of stroke, there is no clear evidence that stroke mediated the association between migraine and VaD and the results for VaD should be interpreted with caution. The sample size for VaD was small, and we noted a nonsignificant trend towards a higher risk of VaD in those with migraines vs. those without. Our analyses thus may be underpowered to determine an effect.

The association between migraines and AD may also be influenced by genetic factors. Individuals with familial AD due to presenilin-1 mutations are more likely to suffer from migraines or recurrent headaches.[42] Research has implicated chromosomes 1 and 19 in both migraines and AD.[43,44] Although neither *APOE* nor *MTHFR* genotype modified the association between migraine and cognitive decline,[40] further studies of these or other genotypes may help to explain the association between migraines and AD and to identify high-risk individuals.

Limitations of this study include self-reported data at baseline, such as the single migraine measure. Migraine data did not include medical records with diagnoses based on standardized migraine criteria (ie, International Headache Society - The International Classification of Headache Disorders II [IHS: ICHD-II]). However, self-reported migraine has been shown to have excellent agreement with the IHS: ICHD-II criteria for migraine diagnoses in a large population-based study.[45] The MSHA migraine measure did not distinguish between migraines with and without aura. Although there are some reports of more severe cognitive consequences in migraines with aura,[4] the effect of aura on the association between migraine and cognitive impairment appears to be inconsistent.[6] This study found a significant association between migraines and AD despite the inclusion of migraine without aura in the general migraine measure. The inclusion of migraine without aura would dilute this effect if migraine with aura causes greater neurological damage, and thus, our findings that individuals with AD were four times more likely to have a history of migraines may be a conservative estimate. However, it is also possible that migraine with aura may have more of an impact on the association between migraine and VaD due to the vascular components of migraine with aura. Nevertheless, significant associations of migraines with AD and all-cause dementia were noted in our study, even with a single, simple migraine measure. Additional data on migraine characteristics, such as use of migraine medications, frequency of migraine attacks, and severity or intensity of migraine attacks, would aid in determining the effects of migraines on cognitive outcomes.[4-6] Differences across migraineurs in factors unrelated to migraine (eg, comorbidities) may also help to explain inconsistent associations between migraines and cognition.[4,6] Although our data on migraine characteristics were limited, analyses did incorporate data on comorbidities, such as depression and cardiovascular disease.

An additional limitation was that the sample was restricted to participants with complete data. Participants who died during the follow-up period (including those with dementia) were not included in the analyses because we could not diagnose cognitive status in those who did not survive until the follow-up assessment. This introduces a potential selection bias that may affect the generalizability of the results. This is a standard limitation of longitudinal studies: the disadvantage of attrition during the follow-up period, however, is generally considered to be outweighed by the advantage of establishing temporality (ie, migraine exposure data were collected before development of dementia as we included only incident dementia cases) compared with cross-sectional study designs. This remains a limitation, however, as loss to follow-up, in particular attrition due to mortality, can influence incidence rates for dementia, as has been demonstrated in this same overall study population.[46]

Although the established higher prevalence of both migraines and dementia in women compared with men is logically reflected in fewer male migraineurs with dementia, the absence in our study of any male participants with migraines who developed dementia meant that it was not feasible to assess effect modification by gender. Clarifying these gender effects on dementia overall as well as subtypes of dementia is an important area for further study. The relatively small number of VaD cases was also a limitation in this study as it decreased the statistical power of the VaD analytic models and precluded the assessment of interactions. Although no effect modification by *APOE* or *MTHFR* genotype has been reported for migraines and cognition,[40] the lack of genetic data to explore potential effect modification for dementia outcomes is also a limitation.

Strengths of this study include data from a large, prospective cohort study. The study design allowed for identification of incident cases of AD, VaD, and all-cause dementia, reducing methodological concerns, such as survival bias, common to studies using prevalent cases. Our population-based sample of older adults living in the community reduced the selection biases common to patient samples restricted to those seeking medical care for migraines or dementia. Whereas previous evidence has primarily been based on these patient populations, we found a significant association of migraine history with increased risk of dementia and AD in a community-dwelling, population-based sample. Clinical assessment and diagnosis were conducted using established criteria. Analyses included consideration of confounding and intervening variables.

5 | CONCLUSIONS

Migraines were a significant risk factor for AD and all-cause dementia in a population-based prospective cohort study of community-dwelling older adults. Evidence did not support an association between migraines and VaD. Identifying predictors of dementia is critical, given the current increases and expected further growth in the proportion of older adults in the population. Identifying a midlife risk factor for dementia, such as migraines, enables earlier detection of at-risk individuals in addition to contributing to our understanding of

AD etiology. It also provides a rationale for the development of new preventive strategies for AD and treatments targeting migraines and associated intervening variables. Implications for clinical practice include earlier screening for cognitive decline in migraine sufferers, as well as more aggressive treatment of potential intervening variables to delay dementia, improve quality of life, and increase the likelihood of healthy aging.

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Conflicts of interest

None declared.

Data availability statement

The data that support the findings of this study are available upon request from the data access committee of the Manitoba Study of Health and Aging. Restrictions apply to the availability of these data, which were used under license for this study. Data are available upon request from the authors with the permission of the data access committee of the Manitoba Study of Health and Aging.

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